REMARKS

Amendments to the Specification

The specification has been amended to include a sequence identifier in the paragraphs beginning at page 19, line 22, and page 30, line 5. No new matter has been added.

Claim Amendments

Claims 35-41 have been cancelled pursuant to the Restriction Requirement. Applicants reserve the right to pursue these claims in a divisional application.

Claim 26 has been amended to recite "inhibiting progression and/or symptoms" instead of "preventing." Support for the amendment can be found, for example, at page 11, lines 1-4. The claim has also been amended to recite that the fibrotic disease is selected from scleroderma, fibrosis of the skin, Dupuytren's contracture, keloid, scarring and fibrosis of the pancreas. Support for the amendment can be found, for example, at page 11, lines 5-18 of the specification. Part (c) of claim 26 to polypeptides comprising 1-4 cysteine-rich domains of osteoprotegerin has been deleted; the subsequent parts of the claim have been designated accordingly. New part (d) of claim 26 has been amended to recite that the mutein has at least 90% identity; support for the amendment can be found at page 15, lines 18-21 of the specification. New part (e) of claim 26 has been amended to recite that the conditions are "12-20°C below the calculated Tm of the hybrid of the DNA sequence of the mutein and the complement in 2 x SSC and 0.5% SDS for 5 minutes" and that the mutein reduces collagen synthesis; support for the amendment can be found at page 14, line 9 through page 15, line 17 of the specification. New part (g) of claim 26 has been amended to simply recite salts and fused proteins of (a) to (f).

Claim 42 has been amended to recite "produced by an isolated cell." Support can be found, for example, in the Examples.

Claims 44, 46 and 48 have been amended to eliminate the dependency to claim 35, which has been cancelled. Claims 49-51 have been amended to depend from claim 48.

No new matter has been added

Status of Claims

Claims 43-47 are indicated in the Office Action as being both under examination and withdrawn from consideration. Claims 43-47 are part of the originally elected group, claims 26-34 and 42-48. Clarification is respectfully requested.

Claims 49-51 have been amended to depend from claim 48, which is presently under examination. Applicants request that claims 49-51 be considered by the Examiner and removed from withdrawn status.

Sequence Rules

The specification is objected to for noncompliance with the Sequence Rules. The Examiner states that the specification refers to sequences on page 19, line 27 and page 30, line 9, but it does not identify the sequences by a sequence identifier. Applicants submit herewith a Substitute Sequence Listing, in which the sequence referenced on page 30 is included as SEQ ID NO: 13 (the sequence referenced on page 19 was included in the original Sequence Listing). In addition, the specification has been amended to include the appropriate sequence identifiers. Withdrawal of the objection is respectfully requested.

Rejection of Claims 26-34 and 42-48 Under 35 U.S.C. § 112, Second Paragraph

Claims 26-34 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter that applicants regard as the invention.

The Examiner asserts that the references to moderately and highly stringent conditions in claim 26 are indefinite. In order to expedite prosecution, the strigency conditions have been explicitly provided in the claims. Reconsideration and withdrawal of the rejection are respectfully requested.

The Examiner states that the recitation "produced by a cell" in claim 42 is indefinite. To expedite prosecution, Applicants adopted the Examiner's suggestion and claim 42 now recites "produced by an isolated cell."

The dependency of claim 48 has been amended to depend only from claim 26.

Reconsideration and withdrawal of the rejection are respectfully requested.

Rejection of Claims 26-34 and 42-48 Under 35 U.S.C. § 112, First Paragraph (Enablement)

Claims 26-34 and 42-48 are rejected 35 U.S.C. § 112, first paragraph, as allegedly failing to meet the enablement requirement. Applicants thank the Examiner for stating that the claims are enabled for a method of treating a fibrotic disease by administering a therapeutically effective amount of a polypeptide comprising SEQ ID NO:2 or SEQ ID NO:4.

The Examiner, however, states that the specification does not reasonably provide enablement for a method of treating and/or preventing a fibrotic disease by administering a polypeptide comprising amino acids 22 to 401 of SEQ ID NO:2 or 4; a polypeptide comprising amino acids 22 to 194 of SEQ ID NO: 2 or 4; a polypeptide comprising one, two three or four cysteine-rich domains of OPG; a mutein of the above polypeptides; or a salt, an isoform, functional derivative, or circularly permutated derivative of the above polypeptides. There are appear to be three aspects to the rejection, namely truncation of the sequence, cysteine-rich domains of OPG, muteins and derivatives of the peptides. Each of these aspects will be addressed below.

Truncation of Polypeptides

Applicants respectfully disagree that the specification is not enabling for administering a polypeptide comprising amino acids 22-401 or amino acids 22-194 of SEQ ID NO:2 or 4. In support, Applicants submit herewith a copy of a Declaration Under 37 C.F.R. § 1.132 ("the Declaration") originally submitted in U.S. Application No. 10/966,845, which simply substantiates the teachings of the application as filed. In the Declaration, Dr. Pierre-Alain Vitte, the Head of Target Pharmacology at Merck Serono International S.A. in Geneva, Switzerland, describes experiments evaluating the efficacy of OPG(N)-Fc, which is a fusion protein composed of the N-terminal residues (1-194) of osteoprotegerin (OPG) and the Fc portion of human IgG1 having preserved effector function. The experiments involve a mouse model of lung fibrosis induced by bleomycin, which corresponds to Example 8 of the instant application and is also an art-recognized animal model to induce fibrosis.

The experiments demonstrate the efficacy of the N-terminal truncated version of OPG. In the experiment, Dr. Vitte states that OPG(N)-Fc, administered at doses of 0.31, 1.25 and 5 mg/kg, significantly reduced bleomycin-induced lung edema, by 15%, 26% and 38%, respectively. In addition, Dr. Vitte reports that a statistically significant reduction of lung fibrosis (-13%, -33% and –35%, $p<0.05$ and 0.01) was observed when OPG(N)-Fc was administered at doses of 0.31, 1.25 and 5 mg/kg, respectively. Furthermore, Dr. Vitte notes that bleomycin-induced-body weight loss was improved when OPG(N)-Fc was administered at doses of 0.31, 1.25 and 5 mg/kg. Taken together, Dr. Vitte states that these results demonstrate that OPG(N)-Fc, administered at doses of 0.31, 1.25 and 5 mg/kg, significantly reduced edema and fibrosis of the lungs that were induced by bleomycin, and furthermore reduced body weight loss.

Based upon the teachings of the specification, one of ordinary skill in the art expect that the N-terminal region of OPG with the amino acids 22-194 is sufficient to induce the anti-fibrotic effect of OPG. The data presented in the Declaration demonstrate that such an expectation is well-founded. Importantly, Dr. Vitte points out that amino acids 1-21 of OPG make up the signal peptide, which is cleaved upon secretion of OPG and is therefore not present in the mature OPG protein *in vivo*. When Dr. Vitte considers the data presented in the Declaration in conjunction with the data present in the application as filed, he expects that a peptide comprising amino acids 22-194

of OPG or a peptide comprising a sequence having at least 90% identity with amino acids 22-194 of OPG would have an anti-fibrotic effect.

In view of the data provided by Dr. Vitte and the conclusions he has drawn therefrom, Applicants believe that the claims are enabled with respect to peptides polypeptide comprising amino acids 22-401 or amino acids 22-194 of SEQ ID NO:2 or 4. The Declaration demonstrates that a fusion protein that includes amino acids 1-194 of OPG (of which SEQ ID NOS: 2 and 4 are isoforms) is effective in treating a model of lung fibrosis. Dr. Vitte pointed out that amino acids 1-21 are simply a signal sequence and are cleaved from OPG *in vivo* upon secretion, such that one of ordinary skill in the art would not expect amino acids 1-21 of SEQ ID NOS: 2 and 4 to contribute any activity. In addition, the Examiner has previously acknowledged in U.S. Application No. 10/966,845 that fibrosis shares a common mechanism among organisms, such that these data should be applicable to fibrosis generally in the claims. Applicants note that these data are also consistent with the remarks made in the first Amendment in U.S. Application No. 10/966,845, in which Applicants cited Simonet *et al.* for the proposition that amino acids 22-194 of OPG are sufficient for biological activity Accordingly, based upon the data in the application and the Declaration, Dr. Vitte's conclusions and the evidence discussed in the prior Amendment, Applicants have provided extensive evidence that one of ordinary skill in the art would have expected a polypeptide comprising either amino acids 22-194 or amino acids 22-401 of SEQ ID NOS: 2 or 4 to be effective in treating fibrosis as of the effective filing date of the instant application.

Cysteine-Rich Domains of OPG

In order to expedite prosecution, references to polypeptides comprising 1-4 cysteine-rich domains of osteoprotegerin have been deleted from the instant claims.

Muteins

Applicants respectfully disagree that the instant claims, as amended, are not enabled with respect to muteins. The claims cover three types of muteins:

d) muteins of (a) to (c), wherein the amino acid sequence has at least 90% identity to at least one of the sequences in (a) to (c);

e) muteins of (a) to (c) which is encoded by a DNA sequence which hybridizes to the complement of the DNA sequence encoding any of (a) to (c) under washing conditions of 12-20°C below the calculated Tm of the hybrid of the DNA sequence of the mutein and the complement in 2 x SSC and 0.5% SDS for 5 minutes and which reduces collagen synthesis; and

f) muteins of (a) to (c) wherein any changes in the amino acid sequence are conservative amino acid substitutions to the amino acid sequences in (a) to (c).

In order to expedite prosecution, mutein d) now requires at least 90% identity to one of the sequences in parts (a) to (c) of the claims. After presenting data on the OPG(N)-Fc fusion protein, Dr. Vitte states in the Declaration that he would expect that a peptide comprising a sequence having at least 90% identity with amino acids 22-194 would have an anti-fibrotic effect. Moreover, in view of the structural recitations in the claims and the structure-function correlations presented in or referenced in the specification, one of ordinary skill in the art could have practiced the claimed invention without undue experimentation as of the effective filing date.

In order to expedite prosecution, mutein e) now recites both structural and functional limitations. Similar to mutein d), in view of the structural and functional recitations in the claims and the structure-function correlations presented in or referenced in the specification, one of ordinary skill in the art could have practiced the claimed invention without undue experimentation as of the effective filing date.

Mutein f) simply covers polypeptides with conservative amino acid substitutions. One of ordinary skill in the art certainly would have expected such polypeptides to be effective in treating fibrosis.

Other Derivatives of OPG

In order to expedite prosecution, part g) of the claim 26 (formerly part h)) has been amended to only cover salts and fused proteins of the polypeptides of (a)-(f). Because a salt or fused protein

does not change the sequence of a polypeptide, one of ordinary skill would have expected a salt or fused protein of a polypeptide of (a)-(f) to have essentially the same activity.

For these reasons, the instant application sufficiently enables claims to treating or inhibiting the progression and/or symptoms of a fibrotic disease for the substances recited in the claims. Reconsideration and withdrawal of the rejection is respectfully requested.

Rejection of Claims 26-34, 42 and 48 Under 35 U.S.C. § 102(e)

Claims 26-34, 42 and 48 are rejected under 35 U.S.C. § 102(e) as allegedly anticipated by Dunstan (US 2006/0019887 A1). The Examiner states that Dunstan teaches the administration of OPG for the treatment of fibrous dysplasia. Claim 26, from which claims 27-34, 42 and 48 depend, has been amended to recite that the fibrotic disease is selected from scleroderma, fibrosis of the skin, Dupuytren's contracture, keloid, scarring and fibrosis of the pancreas. Dunstan does not teach using OPG to teach any of these conditions. Thus, Dunstan does not anticipate claims 26-34, 42 and 48, as amended. Reconsideration and withdrawal of the rejection are respectfully requested.

Rejection of Claims 26-34, 42 and 48 Under 35 U.S.C. § 102(e)

Claims 26-34, 42 and 48 are rejected under 35 U.S.C. § 102(e) as allegedly anticipated by Boyle *et al.* (US 7,005,413). The Examiner states that Boyle *et al.* teach the administration of OPG for the treatment of Paget's disease. Claim 26, from which claims 27-34, 42 and 48 depend, has been amended to recite that the fibrotic disease is selected from scleroderma, fibrosis of the skin, Dupuytren's contracture, keloid, scarring and fibrosis of the pancreas. Boyle *et al.* do not teach using OPG to teach any of these conditions. Thus, Boyle *et al.* do not anticipate claims 26-34, 42 and 48, as amended. Reconsideration and withdrawal of the rejection are respectfully requested.

Double Patenting

Claims 26-34 are provisionally rejected under obviousness-type double patenting as unpatentable over claims 32-66 of co-pending Application No. 10/966,845 in view of Franklin (Biochem. Pharmacol. 49(3):267-273 (1995)). Applicants request that the Examiner hold this rejection in abeyance until this rejection is the sole remaining rejection in either the instant application or Application No. 10/966,845.

CONCLUSION

In view of the above amendment, applicant believes the pending application is in condition for allowance.

If any additional fees are due with this response, please charge our Deposit Account No. 18-1945, under Order No. SLII-P01-001 from which the undersigned is authorized to draw.

Dated: May 7, 2008

Respectfully submitted,

By _____

Jesse A. Fecker, Ph.D.
Registration No.: 52,883
ROPES & GRAY LLP
One International Place
Boston, Massachusetts 02110
(617) 951-7000
(617) 951-7050 (Fax)
Attorneys/Agents For Applicant